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RE: Sympathomimetic drugs should be considered an alternative agent class in refractory chronic urticaria

TO THE EDITOR:

The recent review by Kahn[1] entitled "Alternative Agents in Refractory Chronic Urticaria: Evidence and Considerations on Their Selection and Use" fails to include sympathomimetic agents as an alternative agent class. I believe sympathomimetics should be included as an alternative agent for the following reasons. Historically, ephedrine sulfate has shown some usefulness in the management of chronic idiopathic urticaria (CIU).[2,3] In addition, a 2004 case study by Check et al[4,5] presented 4 cases of CIU that were 100% controlled with the addition of dextroamphetamine sulfate 20-30 mg/d for a minimum treatment duration of 1.7 years and a maximum duration of 13 years. They report 2 additional cases of complete control with dextroamphetamine therapy.[6] Thus, significant improvement occurred in 100% of their 6 cases.

Subsequent to the 2004 publication of the study by Check et al,[4] I incorporated amphetamine salts (Adderall; Shire, Dublin, Ireland) into my therapeutic algorithm for patients with CIU with outstanding results. Since 2004, I have seen 661 patients with urticaria, many of whom have had CIU. My treatment protocol includes a step-up protocol that begins with high-dose H1 antihistamines, H2 antihistamines, antileukotrienes, and finally doxepin. In patients who remain symptomatic in spite of the combination therapy above, Adderall is added in the dose range of 10 to 20 mg, twice daily, and then tapered to the minimal amount to maintain symptomatic control. Since implementing Adderall into my therapeutic regimen, not a single patient with CIU has required oral corticosteroids, cyclosporine, or other ancillary agents to achieve control of their CIU. In addition, I have had 2 patients with a history of failure to respond to cyclosporine therapy who transferred into my practice. In both cases, the addition of Adderall produced immediate relief of their symptoms. In summary, the addition of Adderall in the management of my patients with CIU has produced extraordinary results.

Given the efficacy, beneficial cost, and adverse-effect profile of Adderall when compared with oral corticosteroids, omalizumab, cyclosporine, tacrolimus, mycophenolate, and intravenous immunoglobulin, a trial of dextroamphetamine or amphetamine salts is indicated before the introduction of immunomodular and immunosuppressive agents. In patients without contraindications, sympathomimetics should be considered as alternative agents in the management of CIU and worthy of future clinical trials.

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REPLY:

I thank Dr Miller[1] for his comments regarding the consideration of sympathomimetic drugs as alternative agents in chronic urticaria (CU). The largest amount of literature with sympathomimetic drugs in the treatment of CU involves the use of methylxanthines and β-agonists. The β-agonists have well-known inhibitory effects *in vitro* on mast cells, including inhibition of mediator release. As we noted in a prior review of alternative agents in CU, results of observational studies suggested that terbutaline was effective in therapy for patients with resistant CU; however, 2 double-blind studies have not shown significant benefit of terbutaline in CU.[2] In regard to methylxanthines, a relatively large, double-blind, placebo-controlled study of 134 patients with CU evaluated theophylline 200 mg twice a day for 6 months, then 200 mg once a day for 6 months versus placebo as an add-on therapy to cetirizine.[3] Both groups experienced large improvements in all symptoms

assessed; however, the treatment group had statistically significant improvement in overall urticaria scores but not pruritus. The clinical relevance of this statistical difference is unclear. An observational study of aminophylline plus terbutaline in 42 patients with cold urticaria showed overall improvement in the majority of subjects; however, 3 patients had to stop therapy due to cardiac events, and 19 others had less-severe adverse effects.[4] Overall, small, placebo-controlled studies have not shown efficacy of β-agonists in CU and the evidence for the efficacy of theophylline in CU is modest at best. Nevertheless, these agents may be considered as potential alternative agents in CU.

Amphetamines belong to the class of drugs called b-phenylethylamines and are structurally similar to ephedrine. The pharmacologic effect of amphetamine is predominantly mediated by monoamine release, which is complemented by reuptake inhibition and possibly inhibition of monoamine oxidase that can augment synaptic monoamine concentrations.[5] Enhanced catecholaminergic signaling is thought to be the primary mediator of amphetamine's efficacy in attention deficit hyperactivity disorder. Adderall (Shire, Dublin, Ireland) tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1 and is indicated in the treatment of attention deficit hyperactivity disorder and narcolepsy. Unfortunately, there is virtually no peer-reviewed literature on the efficacy or safety of amphetamines in CU. Miller's anecdotal experience in his practice with Adderall in an unknown number of patients with refractory CU is quite remarkable, with an apparent 100% success rate in avoiding systemic corticosteroids when added to a therapeutic regimen of antihistamines, antileukotrienes, and doxepin. I would certainly encourage Miller to submit his clinical observations with amphetamines in refractory CU for publication. As is true for the vast majority of alternative agents, further well-designed trials are needed to determine the true efficacy and safety of the myriad of alternative agents that have been tried in CU, including amphetamines.

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